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ORIGINAL ARTICLE

Randomized Trial of 2 Versus 1 Dose of Measles Vaccine: Effect on Hospital Admission of Children After 9 Months of Age

Marie Brønd,[1,2] Cesario L. Martins,[1] Stine Byberg,[1,2,3] Christine S. Benn,[2,3] Hilton Whittle,[4] May-Lill Garly,[1] Peter Aaby,[1,2] and Ane B. Fisker[1,2,3]

[1]Bandim Health Project, INDEPTH Network, Bissau, Guinea-Bissau; [2]Research Center for Vitamins and Vaccines (CVIVA), Bandim Health Project, Statens Serum Institut, Copenhagen, Denmark; [3]OPEN, Odense Patient Data Explorative Network, Odense University Hospital/Institute of Clinical Research, University of Southern Denmark; and [4]London School of Hygiene and Tropical Medicine, United Kingdom

Background. Two doses of measles vaccine (MV) might reduce the nonmeasles mortality rate more than 1 dose of MV does. The effect of 2 versus 1 dose on morbidity has not been examined. Within a randomized trial of the effect of 2 doses versus 1 dose of MV on mortality in Guinea-Bissau, we investigated the effect on hospital admissions.

Methods. Children were randomly assigned 1:2 to receive MV at 4.5 and 9 months of age or the currently recommended dose at 9 months. We compared hospital admission rates among children between 9 and 18 months of age in a Cox regression model with age as the underlying time scale. Half of the children had received neonatal vitamin A supplementation (NVAS) in another trial. The beneficial effect of MV at 4.5 and 9 months on mortality was limited to children who had not received NVAS; therefore, we investigated the interaction of MV with NVAS on admission rates.

Results. Among 5626 children (2 doses of MV, 1960 children; 1 dose of MV, 3666), we identified 311 hospital admissions of children between 9 and 18 months of age. Overall, compared to 1 dose of MV, 2 doses reduced the risk of hospital admission for children who had not received NVAS (hazard ratio [HR], 0.66 [95% confidence interval (CI), 0.47–0.93]), but we found no effect among NVAS recipients (HR, 1.16 [95% CI, 0.82–1.63]) ($P = .02$ for interaction).

Conclusions. The benefit of 2 doses of MV was limited to children who had not received NVAS. NVAS is not generally recommended; hence, an early 2-dose measles vaccination policy might reduce hospital admissions more than the current policy of providing the first MV at 9 months of age.

Trial registration. ClinicalTrials.gov identifier NCT00168558.

Keywords. booster doses; heterologous/nonspecific effects; hospital admission; measles vaccine.

In the 1970s, the World Health Organization (WHO) recommended 1 dose of measles vaccine (MV) at 9 months of age as part of the child immunization program in low-income countries [1]. The aim was to protect children against measles infection as early as possible and, at the same time, minimize interference from maternal antibodies. The WHO now recommends a second dose later in life to strengthen immunity against measles. In countries with a national MV coverage below 80%, a first dose is given to children at 9 months of age through the routine vaccination program, and a second dose is given through supplementary vaccination campaigns [2].

The makers of these policies have not considered that MV might have beneficial effects on overall child survival [3–5]. Vaccine effects are thought to be entirely disease specific; vaccines protect against a specific pathogen but do not otherwise affect the immune system. Nonetheless, more and more studies are documenting that childhood vaccines can affect general mortality and morbidity rates [4, 6]; vaccines seem to alter the susceptibility to other pathogens as well as the targeted ones. These effects have been coined heterologous or nonspecific effects (NSEs) [3]. The WHO recently reviewed the evidence for NSEs, and concluded that additional research is warranted [7, 8].

On the basis of many observational studies and natural experiments, MV seems to confer beneficial NSEs, which might be stronger the earlier the vaccine is given. To test the effect of an early dose of MV on child mortality rates, we conducted a large-scale randomized trial from 2003 to 2009 by randomly allocating children to receive MV at 4.5 and 9 months or the currently recommended single dose of MV at 9 months of age. In the per-protocol analysis, 2 doses of MV were associated with a mortality hazard ratio (HR) of 0.70 (95% confidence interval [CI], 0.52–0.94) for children between 4.5 and 36 months of age; this effect was stronger for girls. Between 9 and 36 months

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Correspondence: A. B. Fisker, MD, PhD, Research Center for Vitamins and Vaccines (CVIVA), Bandim Health Project, Statens Serum Institut, Artillerivej 5, 2300 Copenhagen S, Denmark (abf@ssi.dk).

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of age, the HR was 0.71 (95% CI, 0.50–1.01) for children who had received 2 doses versus those who had received 1 dose of MV [4]. A large proportion of the participating children had previously taken part in a trial of neonatal vitamin A supplementation (NVAS) [9–11]. The reduction in mortality rate was found only for children who had not received NVAS (HR, 0.50 [95% CI, 0.32–0.78] for children between 4.5 and 36 months of age and 0.56 [95% CI, 0.34–0.93] for those between 9 and 36 months of age) [4].

A secondary outcome was the all-cause hospital admission rate. We found that early MV compared with no early MV reduced the all-cause hospital admission rate in children between 4.5 and 9 months of age (HR, 0.70 [95% CI, 0.52–0.95]). The beneficial effect was again strongest for children who had not received NVAS (HR, 0.53 [95% CI, 0.34–0.84]). Furthermore, the effect was particularly strong for children with a respiratory infection (HR, 0.37 [95% CI, 0.16–0.89]) and for those enrolled in the dry season (HR, 0.53 [95% CI, 0.33–0.86]) [6].

In the present study, we used the trial data to investigate whether 2 doses of MV with or without NVAS compared with the currently recommended 1 dose of MV at 9 months of age had an effect on hospital admissions of children between 9 and 18 months of age. Because we previously observed that the effect of MV varies according to sex, NVAS, and season, we also conducted prespecified analyses stratified according to these factors [4, 6].

METHODS

Setting and Study Population

The trial was conducted in the Bandim Health Project's (BHP) study area, which covers roughly 100 000 inhabitants, approximately 30% of the population in Bissau, the capital of Guinea-Bissau [12]. Since 1978, the BHP has maintained a health and demographic surveillance system through which all houses are visited every month to register new pregnancies and births. All newborns are assigned a unique identification number to facilitate follow-up. Children younger than 3 years are visited at home every third month so that information about breastfeeding, hospital admissions in the previous 3 months, vaccinations, residence, and vital status can be collected. Bissau experienced a measles epidemic between May 2003 and May 2004 [13], but no cases of measles were reported in 2005 and 2006 [14].

The 2-Dose MV Trial

The trial has been described in detail elsewhere [4]. The trial was conducted in 2003–2009 and aimed to assess the effect of different MV schedules and vaccine strains on the overall mortality rate of children between 4.5 and 36 months of age. The sample size was based on the hypothesis that an additional early MV dose would reduce the mortality rate in children between 4.5 and 36 months of age by 25%; we hypothesized a priori that the beneficial effect would be strongest for girls and for children enrolled in the dry season (December to May). Children were eligible for enrollment in the study at 4.5 months of age, 4 weeks after having received their third diphtheria-tetanus- pertussis (DTP) vaccine. Identified through the BHP routine registration system, eligible children and their mothers/guardians were invited to the local health center. At the health center, children underwent an examination by a medical doctor, and the mothers/guardians received a verbal and written explanation of the study. For sick children judged to be in need of hospital admission, enrollment was deferred until the child had recovered. Once consent was provided, each child were assigned randomly to 1 of 3 groups for different MV strains and numbers of MV doses, that is, 2 doses of standard-dose Edmonston-Zagreb (EZ) MV at 4.5 and 9 months of age (group A), standard-dose EZ MV at 9 months of age (group B), or standard-dose Schwarz (SW) MV at 9 months of age (group C). Children in groups B and C were assigned randomly to receive a booster dose of the same strain of MV at 18 months of age. All children were invited back to the health center at the age of 9 months to receive a MV.

In our analysis, we included children who had received the 9-month MV from the study team. We followed up the children until 18 months of age and compared recipients of 2 doses of MV at 4.5 and 9 months of age with recipients of 1 dose of MV at 9 months of age.

The NVAS trials enrolled newborns between 2002 and 2008. Two trials were conducted among children with normal birth weight (≥2500 g) and randomly assigned them to receive vitamin A (50 000 [9] or 25 000/50 000 IU [11]) or placebo at the time of Bacillus Calmette–Guérin (BCG) vaccination. A third trial randomly assigned low-birth-weight infants (<2500 g) to receive NVAS (25 000 IU) or placebo and to receive early BCG vaccine or the normal delayed BCG vaccine in a 2-by-2 factorial design [10].

Information on Hospital Admissions

The BHP maintains a registration system at the National Hospital Simão Mendes (NHSM). Registration includes identification number, name, date of birth, and vaccination status for all children admitted to the pediatric ward. We used the identification number to link the hospital and trial data to identify the trial participants who had been admitted between 9 and 18 months of age. We cross-checked the hospital data against the data from the 3-monthly routine visits to identify mothers of trial participants who had reported a hospital admission at one of the 3-monthly routine home visits if any part of the reporting period was in the age span 9–18 months. If the mother reported an admission that was not already identified in the hospital data, we performed a manual search of the hospital data using the child's name, mother's name, address, date of birth, and identification numbers from other trials. We identified 311 admissions of children to the NHSM between 9 and 18 months

of age. In addition, mother/caretakers reported 206 admissions that could not be identified in the records from NHSM and 47 admissions that were identified but not included in the analyses because the children were outside the age span of interest. The rate of unidentified admissions did not differ according to group (76 in the 2-dose group, 130 in the 1-dose group; $P = .27$). These admissions might have occurred at 1 of the minor hospitals in Bissau or might have been reported because the mother/caretaker interpreted treatment in an outpatient service as an admission [6]. Also, there might have been recall bias. Finally, because routine visits are organized according to place of residence rather than age of the child, some maternally reported admissions occurred before 9 months or after 18 months of age. Because the nature and the timing of the unidentified admissions were uncertain, we included in our analysis only admissions identified at the NHSM.

After identifying admission records of trial participants in the NHSM database, we used information regarding diagnosis, date of admission, and date of discharge for additional analyses. For any child who had received more than 1 diagnosis, the primary diagnosis was used. The exception to this was cases in which the primary diagnosis was an underlying disease (malnutrition or heart malformation) or unspecified fever; 6 admissions were classified according to the secondary diagnosis. The availability of paraclinic diagnostic tools are limited at the NHSM. The 3 most commonly used diagnostic categories were respiratory infection, malaria/anemia, and diarrhea/dysentery.

Statistical Analyses

We compared the distribution of background variables obtained at the 9-month health center visit using t tests for continuous normally distributed variables, the rank-sum test for non-normally distributed variables, and the χ^2 test for categorical variables.

The hospital admission rates of children did not differ between those who received 1 of the 2 different vaccine strains in the 1-dose groups (B and C) (7.6 per 100 person-years for EZ strain recipients and 8.9 per 100 person-years for SW strain recipients) (HR, 0.85 [95% CI, 0.65–1.11]). As in the previous analyses [4], these 2 groups were combined.

We compared the admission rates of children who received 2 doses and those who received 1 dose of MV in a Cox proportional hazards model with age as the underlying time scale and allowing for repeated events. Children were at risk of hospitalization from the date they received the 9-month MV from the study team until hospital admission, death, migration, or 18 months of age, whichever came first. Children who moved out of the area were censored on the date of migration. Data were analyzed overall and according to disease category.

Many of the children enrolled in the MV trial were also enrolled in a randomized controlled trial of NVAS in which they were randomly assigned to receive NVAS or placebo [9–11]. Because NVAS interacted with vaccinations and neutralized the beneficial effect of an early MV on mortality rates [4, 15], we stratified the analyses for NVAS status and report results for recipients and nonrecipients of NVAS separately.

We had hypothesized that the effect of MV on mortality rates would be stronger for girls than for boys [4, 6] and for children who receive MV in the dry season [6]. Hence, we examined whether sex and season modified the effect of MV. In an explorative analysis, we investigated the effects of 2 versus 1 dose in the period after a measles epidemic.

Of the 6648 children enrolled in the trial, 231 were excluded because of measles infection before enrollment or errors in timing of enrollment, which left 6417 children for the main analysis [4, 6]. All analyses were conducted using Stata 13.

Ethical Approval

The protocol for the 2-dose trial was approved by the Guinean Ministry of Health's Research Coordination Committee, the Gambian/MRC scientific and ethics committees, and the Danish Central Ethical Committee. This trial was registered at ClinicalTrials.gov under identifier NCT00168558.

RESULTS

Participant Flow

Of the 6471 children enrolled at 4.5 months of age between August 2003 and April 2007 and included in the main analysis [4, 6], 5907 (92%) were seen and vaccinated against measles by the BHP at a health center at 9 months of age or had received MV elsewhere (1979 [93%] in the 2-dose group and 3928 [92%] in the 1-dose control group) (Figure 1). More children in the control group had received the MV elsewhere before 9 months of age [4]. The following analyses were restricted to the 5626 children who had followed the protocol and received the 9-month MV administered by the BHP (Table 1). No statistically significant differences existed between the 2 randomly assigned groups with regard to background factors except for a slight difference in age; the median age at the 9-month vaccination was 274 days in the 2-dose group and 273 days in the 1-dose group ($P = .01$) (Table 1). Forty-nine percent (2734 of 5626) of the children had received NVAS.

Main Results

We identified 311 hospital admissions at HNSM, which resulted in an overall hospital admission rate of 7.8 per 100 person-years. The effect of 2 doses of MV differed significantly between nonrecipients and recipients of NVAS ($P = .02$ for interaction) (Table 2). Among children in the 2-dose MV group who had not received NVAS, we found a 34% reduction in the hospital admission rate (HR, 0.66 [95% CI, 0.47–0.93]). In contrast, there was no effect for those who had received NVAS (HR, 1.16 [95% CI, 0.82–1.63]). The patterns were similar for boys and girls

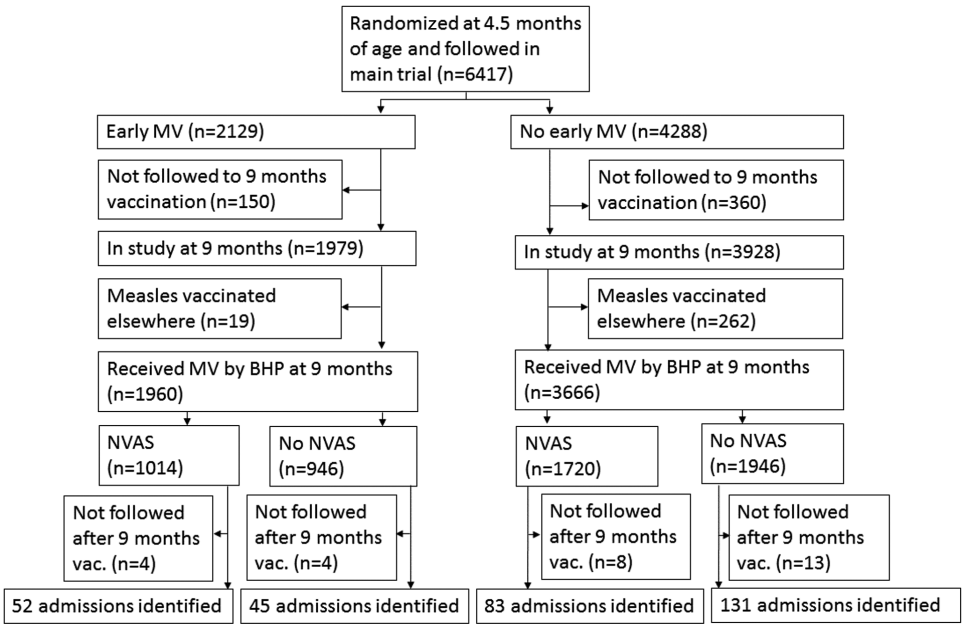

Figure 1. Participant flow. Abbreviations: BHP, Bandim Health Project; MV, measles vaccine; NVAS, neonatal vitamin A supplementation.

(Table 2). The 311 admissions occurred among 289 children. After we censored the follow-up period after the first admission, the HRs were 0.58 (95% CI, 0.37–0.93) among the children who had not received NVAS and 1.09 (95% CI, 0.69–1.71) among those who had received NVAS (P = .06 for interaction between NVAS and 2 doses of MV).

Only 2 admissions that resulted from measles infection were found; hence, censoring measles admissions had no effect on the estimates for 2 versus 1 dose of MV (Table 2). One of the children admitted with measles had received the 9-month vaccination 3 days before admission, so the admission is unlikely to represent vaccine failure; instead, the child had been vaccinated in the incubation period. When the analysis was limited to children who had received the 9-month vaccination after June 1, 2004 (after the measles epidemic), the HRs were 0.63 (95% CI, 0.44–0.91) among children who had not received NVAS and 1.19 (95% CI, 0.83–1.71) among those who had received NVAS (P = .02 for interaction between NVAS and 2 doses of MV). The beneficial effects of 2 versus 1 dose among NVAS nonrecipients were separately significant for children enrolled in the dry season (December through May) (HR, 0.59 [95% CI, 0.37–0.94]) but not for children enrolled in the rainy season (June through November) (HR, 0.75 [95% CI, 0.45–1.24]) (P = .49 for interaction with season) (Supplementary Table 1). Season of the 9-month vaccination might also have had an effect; among children who had not received NVAS and received the 9-month MV in the rainy season, 2 doses of MV, compared with 1 dose, was associated with an HR of 0.53 (95% CI, 0.32–0.85). For the corresponding children who received their 9-month MV in the dry season, 2 doses of MV were associated with an HR of 0.85 (95% CI, 0.53–1.37) (P = .17 for interaction with season of the 9-month vaccination) (Supplementary Table 2). However, season of enrollment and season of the 9-month vaccination were highly correlated; 76% of the children enrolled in the dry season received their 9-month MV in the rainy season.

Causes of Hospital Admissions

The 2 groups did not differ with regard to length of hospital stay; the median time was 7 days in both groups (data not shown). The 3 main disease categories of hospital admissions were malaria/anemia (49%), respiratory infection (33%), and diarrhea/dysentery (14%). These 3 causes of admission accounted for 96% of all hospital admissions; therefore, we stratified our analyses according to these 3 causes of hospital admission. Among the children who did not receive NVAS, 2 doses of MV tended to reduce the hospital admission rates related to each of the 3 categories of diseases (Table 3).

Thirty admissions had a fatal outcome. When we censored admissions with a fatal outcome, the 2-dose MV policy tended to result in a reduction of the nonfatal admission rate (HR, 0.74 [95% CI, 0.52–1.05]) among children who had not received NVAS but not among the children who had received NVAS (HR, 1.18 [95% CI, 0.82–1.70]) (P = .07 for interaction with NVAS status).

DISCUSSION

As in our previous analyses of mortality rates and hospital admissions before 9 months of age [4, 6], 2 doses of MV had

Table 1. Background Factors for Children Who Received Early 2-Dose MV and MV at 9 Months

Factor	2 Doses of MV[a]	1 Dose of MV[a]	*P*
n	1960	3666	
Boys	51 (998/1960)	50 (1826/3666)	.43
Age at which child was seen for 9-mo visit (median [IQR; N]) (days)	274 (271–278; 1960)	273 (271–276; 3666)	.01
District			
Bandim	42 (824/1960)	43 (1569/3666)	.86
Belem	19 (363/1960)	18 (670/3666)	
Cuntum	39 (773/1960)	39 (1427/3666)	
Ethnicity			
Balanta	9 (178/1960)	10 (350/3666)	.60
Fula/Mandiga	23 (441/1960)	23 (859/3666)	
Manjaco/Mancanha	21 (415/1960)	22 (816/3666)	
Pepel	31 (605/1960)	29 (1051/3666)	
Other	16 (320/1960)	16 (588/3666)	
Missing	0 (1/1960)	0 (2/3666)	
Age of mother at birth of child (mean [SD; N]) (y)	26.0 (6.1; 1871)	26.1 (6.2; 3515)	.28
Socioeconomic factors			
People sleeping in bed of the child (median [IQR; N])	3 (3–3; 1954)	3 (3–3; 3645)	.47
People sleeping in room of the child (median [IQR; N])	4 (3–5; 1952)	4 (3–5; 3645)	.07
Had electricity installed in the house	43 (850/1958)	41 (1505/3648)	.11
Had working electricity in the house	63 (524/1947)	66 (977/1487)	.10
Had pigs at household	19 (367/1941)	18 (664/3628)	.58
Had pigs in the house	33 (638/1938)	32 (1173/3616)	.72
Had antimalarial medicine at home	39 (748/1929)	37 (1346/3595)	.33
Had toilet inside	16 (307/1959)	15 (535/3657)	.30
Anthropometric factors			
Weight (mean [SD; N]) (kg)	8.41 (1.17; 1959)	8.36 (1.16; 3665)	.15
Length (mean [SD; N]) (cm)	70.2 (3.3; 1960)	70.1 (3.2; 3666)	.26
MUAC (mean [SD; N]) (cm)	14.6 (1.2; 1958)	14.5 (1.3; 3663)	.60
Had BCG scar	86 (1686/1958)	85 (3115/3666)	.31
Morbidity			
Had fever on day of the 9-mo visit	5 (102/1932)	6 (206/3613)	.53
Had diarrhea on day of the 9-mo visit	3 (63/1937)	3 (110/3631)	.65
In an NVAS trial	85 (1658/1960)	85 (3133/3666)	.38
Vita1 (>2500 g, 50 000 IU vs placebo)	34 (662/1960)	34 (1247/3666)	.85
Vita2 (≤2500 g, 25 000 IU vs placebo)	6 (119/1960)	6 (224/3666)	.95
Vita3 (>2500 g, 50 000/25 000 IU vs placebo)	47 (913/1960)	47 (1740/3666)	.53

Abbreviations: BCG, Bacillus Calmette–Guérin; IQR, interquartile range; MUAC, mid-upper-arm circumference; MV, measles vaccine; NVAS, neonatal vitamin A supplementation.
[a]Unless stated otherwise, values shown are percentage (n/N).

Table 2. Hospital Admission Rates Between 9 and 18 Months of Age for Children Who Received 2 or 1 Dose of MV, and Admission HRs for Those Who Received 2 Compared With 1 Dose of MV, According to NVAS Status and Sex

	2 Doses of MV		1 Dose of MV		Admission HR (95% CI)	
NVAS Status and Sex	Admission Rate/100 Person-Years (Admissions/Person-Days)	N	Admission Rate/100 Person-Years (Admissions/Person-Days)	N	All Admissions	Excluding Measles Admissions
No NVAS						
Male	6.3 (23/229 630)	513	10.0 (67/243 900)	938	0.63 (0.39–1.01)	0.64 (0.40–1.03)
Female	6.3 (22/219 999)	497	9.1 (64/256 783)	995	0.69 (0.43–1.12)	0.70 (0.43–1.14)
Overall	6.3 (45/449 628)	1010	9.6 (131/500 683)	1933	0.66 (0.47–0.93)	0.67 (0.48–0.94)
NVAS						
Male	8.8 (30/124 018)	481	7.3 (46/133 073)	877	1.21 (0.76–1.91)	1.21 (0.76–1.91)
Female	6.7 (22/120 290)	461	6.1 (37/128 277)	835	1.09 (0.64–1.85)	1.09 (0.64–1.85)
Overall	7.8 (52/244 308)	942	6.7 (83/261 350)	1712	1.16 (0.82–1.63)	1.15 (0.82–1.63)
Both groups						
Male	7.5 (53/257 091)	994	8.7 (113/473 530)	1815	0.87 (0.62–1.20)	0.87 (0.63–1.21)
Female	6.4 (44/248 567)	958	7.7 (101/476 781)	1830	0.84 (0.59–1.19)	0.85 (0.59–1.21)
Overall	7.0 (97/505 658)	1952	8.2 (214/950 311)	3645	0.85 (0.67–1.09)	0.86 (0.68–1.10)

Abbreviations: CI, confidence interval; HR, hazard ratio; MV, measles vaccine; NVAS, neonatal vitamin A supplementation.

Table 3. Number of Hospital Admissions[a] Between 9 and 18 Months of Age for Children Who Received 2 or 1 Dose of MV, and Admission HRs for Those Who Received 2 Compared With 1 Dose of MV, According to Diagnosis and Sex

	Admitted Children According to Sex and Vaccination Group (n [No NVAS; NVAS)]								
	Boys		Girls		Both Groups		Admission HR (95% CI)		
Diagnosis	2 Doses of MV	1 Dose of MV	2 Doses of MV	1 Dose of MV	2 Doses of MV	1 Dose of MV	No NVAS	NVAS	Both Groups
Respiratory infection	15 (6; 9)	43 (25; 18)	16 (10; 6)	28 (18; 10)	31 (16; 15)	71 (43; 28)	0.72 (0.40–1.27)	0.99 (0.53–1.85)	0.82 (0.54–1.26)
Diarrhea/dysentery	8 (3; 5)	13 (9; 4)	5 (3; 2)	18 (13; 5)	13 (6; 7)	31 (22; 9)	0.52 (0.21–1.28)	1.43 (0.58–3.83)	0.78 (0.41–1.50)
Malaria/anemia	29 (14;15)	53 (31;22)	21 (9; 12)	50 (31; 19)	50 (23; 27)	103 (62; 41)	0.71 (0.44–1.15)	1.21 (0.75–1.97)	0.91 (0.65–1.28)
Any of the 3 main causes	52 (33;29)	109 (65;44)	42 (22;20)	96 (62;34)	94 (45;49)	205 (127;78)	0.68 (0.48–0.96)	1.16 (0.81–1.65)	0.86 (0.68–1.10)

Abbreviations: CI, confidence interval; HR, hazard ratio; MV, measles vaccine; NVAS, neonatal vitamin A supplementation.

[a]Admissions attributable to measles (2), accidents (1), and other causes (9) malnutrition (1), febrile syndrome (1), abscess (2), nephritis (1), urosepticemia (1), asthma (2), skin infection (1) not shown.

a significant beneficial effect among children who had not received NVAS, whereas there was no effect among NVAS recipients. Hence, priming at birth with NVAS continued to have an effect on how the children responded to interventions after 9 months of age. The benefit of 2 doses of MV was not explained by better protection against measles infection.

Study Strengths and Weaknesses

A major strength of this study is its randomized design and the large number of participants included. Because the randomization took place at 4.5 months of age, a risk that the 2 groups were no longer comparable at 9 months of age existed; more children in the control group died. More children were vaccinated by others than the study team. However, we found no differences in background factors between the groups at 9 months of age; the 2 groups were essentially comparable at the beginning of follow-up. The only factor that differed significantly was the age at the 9-month visit, but the difference was small, and because age was an underlying time scale in our analyses, we adjusted for it; thus, bias should not have been introduced. Because of the higher mortality rate in the control group before 9 months of age [4], the group might have been left with fewer frail children with a higher admission risk. However, this attrition would tend to mask any benefit of the intervention and thus does not explain the observed benefit among children who had not received NVAS.

The study was not blinded with respect to the number of MVs the children had received. The staff at the pediatric ward could have looked at the children's vaccination card to determine vaccination status. However, standard procedures at the pediatric department does not involve checking a vaccination card and it is unlikely that the medical staff made decisions on admission that depended on an extra dose of early MV if they inspected the vaccination card. If the staff had reacted differently depending on vaccination status, we would have expected to find the same trends among those who had received NVAS and those who had not, because randomization to NVAS or placebo group was blinded. Because this was not the case, we have no reason to think that the medical staff made biased decisions that affected the outcome of the study.

Consistencies With Previous Studies

The effect of repeated doses of MV on morbidity had not been studied previously. A few studies assessed the effect of 2 versus 1 dose of MV on mortality rates. In our trial, the mortality rate was lower among children aged 9 to 36 months who had received 2 doses than among those who had received only 1 dose of MV, if they had not received NVAS [4]. A beneficial effect on mortality rates of receiving a booster MV dose was also found in a study from Guinea-Bissau in the early 1980s when the first MVs were given in campaigns. Children who received 2 doses of MV before and after 9 months had a 59% (95% CI, 15%–81%) lower mortality rate between 9 and 59 months of age than children who received only 1 dose after 9 months [16]. After a national MV campaign in Guinea-Bissau in 2006, children who had received a routine MV and a campaign MV had a 41% (95% CI, 1%–64%) lower mortality rate than children who had received only the routine MV in the 2 preceding years [17].

MV (versus no MV) was shown previously to protect against hospital admissions. In a study from Guinea-Bissau, the risk of hospital admission among children aged 9 to 17 months who presented for outpatient consultation was assessed according to the most recently received vaccine. The HR of hospital admission was 0.72 (95% CI, 0.63–0.86) for children who had received MV after DTP as their most recent vaccine, compared with children who had DTP as the most recent vaccine [18]. Hence, MV might lower the severity of infections and therefore reduce the risk of hospital admission. Using national registry data from Denmark, vaccination against measles, mumps, and rubella (MMR) after receiving a DTP-containing vaccine was associated with an admission ratio of 0.86 (95% CI, 0.84–0.88) compared with receiving the DTP-containing vaccine as the most recent vaccine [19]. The effect was particularly strong for lower respiratory infection (admission ratio, 0.80 [95% CI, 0.79–0.84]), and MMR vaccination was also associated with lower admission rates for respiratory syncytial virus infection [20]. Hence, in both high- and low-income countries, measles-containing vaccines might reduce the number of hospital admissions for respiratory syncytial virus and other respiratory infections.

For children from 4.5 to 9 months of age, receiving an early MV (versus no MV) was associated with a lower risk of hospital admission for children who had not received NVAS [6]. This pattern was seen also when follow-up was extended to 18 months of age after all children had received the 9-month MV. Hence comparing 2 doses versus 1 dose of MV. Although the results of previous studies suggest that the beneficial effect of MV (compared with no MV) is particularly strong for lower respiratory infection, when the control group had received MV [6, 19, 20], no clear indication that the benefit of a booster dose was linked to a specific disease group was found.

Interpretation

The most important aspect of this study is that an additional dose of MV might provide additional beneficial NSEs that protect against hospital admission. If the beneficial NSEs were a result of specific effects, we should have found little difference in admission patterns between the 2 groups after the 9-month vaccination, because both groups had received MV, and 1 dose normally offers sufficient protection against severe measles leading to admission [21]. Furthermore, excluding the period of the measles epidemic should have weakened the difference between the randomization groups, but such was not the case. Thus, results of this study suggest that an extra dose of MV boosts beneficial NSEs. We have also found beneficial boosting effects of other live vaccines [3, 22]. Such boosting effects were not taken into consideration when planning current vaccination policies. Because the most recent trials of NVAS found few or no beneficial effects of NVAS [23–26], NVAS is unlikely to become general policy. Therefore, our estimates for the group who did not receive NVAS will represent the expected effect of an additional dose of MV.

The mechanism behind the observed nonspecific benefits of an additional dose of MV is unknown. We previously showed that providing MV in the presence of maternal measles-specific antibodies results in lower attained antibody levels but, at the same time, stronger beneficial NSEs [27]. We speculate that the mechanism could be based on antibody-antigen complexes that enhance T-cell responses or produce broader responses with more cross-reactivity [27]. Given that VAS is a potent immune stimulator that can cause epigenetic alterations [28], the effect might differ according to NVAS status.

The WHO recommends 2 doses of MV. The first dose should be given as soon as possible after the loss of protection by maternal antibodies, and the second dose could be given at a specific age or through mass campaigns targeted at defined age groups. In countries with ongoing measles transmission and where the risk of death as a result of measles is high, the WHO recommends the first MV dose at 9 months and a second dose in the second year of life [2]. However, with beneficial NSEs leading to a lower mortality rate and less severe morbidity, an earlier dose of MV and a booster dose at 9 months of age might be preferable. Furthermore, several studies [29–32] found that maternal antibodies wane well before a child is 9 months old; hence, it might be appropriate to recommend the MV before 9 months of age also for optimal measles protection.

CONCLUSION AND PERSPECTIVES

The results of our study suggest that a 2-dose schedule with an early MV at 4.5 months of age followed by a booster MV at 9 months of age can reduce the number of hospital admissions in low-income countries such as Guinea-Bissau. A 2-dose MV regime prevents early measles infection [21], reduces hospital admissions [6], and improves child survival [4] as results of a combination of the specific and nonspecific beneficial effects of MV.

Supplementary Data

Supplementary materials are available at Journal of *the Pediatric Infectious Diseases Society* online.

Notes

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References

1. Expanded Programme on Immunizations. The optimal age for measles immunization. Wkly Epidemiol Rec **1982**; 57:89–91.
2. Measles vaccines: WHO position paper. Wkly Epidemiol Rec **2009**; 84:349–60.
3. Benn CS, Netea MG, Selin LK, Aaby P. A small jab - a big effect: nonspecific immunomodulation by vaccines. Trends Immunol **2013**; 34:431–9.
4. Aaby P, Martins CL, Garly ML, et al. Non-specific effects of standard measles vaccine at 4.5 and 9 months of age on childhood mortality: randomised controlled trial. BMJ **2010**; 341:c6495.
5. Aaby P, Garly ML, Balé C, et al. Survival of previously measles-vaccinated and measles-unvaccinated children in an emergency situation: an unplanned study. Pediatr Infect Dis J **2003**; 22:798–805.
6. Martins CL, Benn CS, Andersen A, et al. A randomized trial of a standard dose of Edmonston-Zagreb measles vaccine given at 4.5 months of age: effect on total hospital admissions. J Infect Dis **2014**; 209:1731–8.
7. Higgins JPT, Soares-Weiser K, Reingold A. Systematic review of the non-specific effects of BCG, DTP and measles containing vaccines. Available at: http://www.who.int/immunization/sage/meetings/2014/april/3_NSE_Epidemiology_review_Report_to_SAGE_14_Mar_FINAL.pdf?ua=1, **2014**. Accessed May 28, 2017.
8. World Health Organization. Meeting of the Strategic Advisory Group of Experts on immunization, April 2014—conclusions and recommendations. Wkly Epidemiol Rec **2014**; 89:221–36.
9. Benn CS, Diness BR, Roth A, et al. Effect of 50,000 IU vitamin A given with BCG vaccine on mortality in infants in Guinea-Bissau: randomised placebo controlled trial. BMJ **2008**; 336:1416–20.

10. Benn CS, Fisker AB, Napirna BM, et al. Vitamin A supplementation and BCG vaccination at birth in low birthweight neonates: two by two factorial randomised controlled trial. BMJ **2010**; 340:c1101.
11. Benn CS, Diness BR, Balde I, et al. Two different doses of supplemental vitamin A did not affect mortality of normal-birth-weight neonates in Guinea-Bissau in a randomized controlled trial. J Nutr **2014**; 144:1474–9.
12. Aaby P. Bandim: an unplanned longitudinal study. In: Das Gupta M, Aaby P, Pison G, Garenne M, eds. Prospective community studies in developing countries. Oxford, England: Oxford University Press, **1997**: pp 276–96.
13. Balé C, Garly ML, Martins C, et al. Risk factors for measles in young infants in an urban African area with high measles vaccination coverage. Pediatr Infect Dis J **2011**; 30:689–93.
14. World Health Organisation. Measles reported cases. Available at: http://apps.who.int/immunization_monitoring/globalsummary/timeseries/tsincidencemeasles.html. Accessed May 28, 2017.
15. Benn CS, Martins CL, Fisker AB, et al. Interaction between neonatal vitamin A supplementation and timing of measles vaccination: a retrospective analysis of three randomized trials from Guinea-Bissau. Vaccine **2014**; 32:5468–74.
16. Aaby P, Andersen M, Sodemann M, et al. Reduced childhood mortality after standard measles vaccination at 4–8 months compared with 9–11 months of age. BMJ **1993**; 307:1308–11.
17. Fisker AB, Rodrigues A, Martins C, et al. Reduced all-cause child mortality after general measles vaccination campaign in rural Guinea-Bissau. Pediatr Infect Dis J **2015**; 34:1369–76.
18. Biai S, Rodrigues A, Nielsen J, et al. Vaccination status and sequence of vaccinations as risk factors for hospitalisation among outpatients in a high mortality country. Vaccine **2011**; 29:3662–9.
19. Sørup S, Benn CS, Poulsen A, et al. Live vaccine against measles, mumps, and rubella and the risk of hospital admissions for nontargeted infections. JAMA **2014**; 311:826–35.
20. Sørup S, Benn CS, Stensballe LG, et al. Measles-mumps-rubella vaccination and respiratory syncytial virus-associated hospital contact. Vaccine **2015**; 33:237–45.
21. Martins CL, Garly ML, Balé C, et al. Protective efficacy of standard Edmonston-Zagreb measles vaccination in infants aged 4.5 months: interim analysis of a randomised clinical trial. BMJ **2008**; 337:a661.
22. Benn CS, Fisker AB, Whittle HC, Aaby P. Revaccination with live attenuated vaccines confer additional beneficial nonspecific effects on overall survival: a review. EBioMedicine **2016**; 10:312–7.
23. Mazumder S, Taneja S, Bhatia K, et al. Efficacy of early neonatal supplementation with vitamin A to reduce mortality in infancy in Haryana, India (Neovita): a randomised, double-blind, placebo-controlled trial. Lancet **2015**; 385:1333–42.
24. Masanja H, Smith ER, Muhihi A, et al. Effect of neonatal vitamin A supplementation on mortality in infants in Tanzania (Neovita): a randomised, double-blind, placebo-controlled trial. Lancet **2015**; 385:1324–32.
25. Edmond KM, Newton S, Shannon C, et al. Effect of early neonatal vitamin A supplementation on mortality during infancy in Ghana (Neovita): a randomised, double-blind, placebo-controlled trial. Lancet **2015**; 385:1315–23.
26. Soofi S, Ariff S, Sadiq K, et al. Evaluation of the uptake and impact of neonatal vitamin A supplementation delivered through the Lady Health Worker programme on neonatal and infant morbidity and mortality in rural Pakistan: an effectiveness trial. Arch Dis Child **2017**; 102:216–23.
27. Aaby P, Martins CL, Garly ML, et al. Measles vaccination in the presence or absence of maternal measles antibody: impact on child survival. Clin Infect Dis **2014**; 59:484–92.
28. Arts RJ, Blok BA, van Crevel R, et al. Vitamin A induces inhibitory histone methylation modifications and down-regulates trained immunity in human monocytes. J Leukoc Biol **2015**; 98:129–36.
29. Garly ML, Balé C, Martins CL, et al. Measles antibody responses after early two dose trials in Guinea-Bissau with Edmonston-Zagreb and Schwarz standard-titre measles vaccine: better antibody increase from booster dose of the Edmonston-Zagreb vaccine. Vaccine **2001**; 19:1951–9.
30. Martins C, Bale C, Garly ML, et al. Girls may have lower levels of maternal measles antibodies and higher risk of subclinical measles infection before the age of measles vaccination. Vaccine **2009**; 27:5220–5.
31. Leuridan E, Hens N, Hutse V, et al. Early waning of maternal measles antibodies in era of measles elimination: longitudinal study. BMJ **2010**; 340:c1626.
32. Gagneur A, Pinquier D, Aubert M, et al. Kinetics of decline of maternal measles virus-neutralizing antibodies in sera of infants in France in 2006. Clin Vaccine Immunol **2008**; 15:1845–50.